

Neurochemical profiles of hearing loss, tinnitus and distress using non-invasive Magnetic Resonance techniques

Section 1 – Project Details:

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Rationale:

Tinnitus affects about 20% of the adult population and can be extremely distressing.^{1,2} When asked, patients say they want a cure to silence tinnitus and that they are dissatisfied with current approaches which merely help patients to manage the symptoms and learn to live with the noise [personal communication, British Tinnitus Association]. At present, there is no singularly effective treatment and no licensed drugs for tinnitus.

Development of new treatments is hampered by a poor understanding of the pathophysiology of tinnitus and how it differs from that of hearing loss. It's likely that the condition has different causes and hence different routes to personalised therapeutic solutions. Human research is more likely to progress this search for a cure, since there is not yet any consensus for an adequate animal model.

Our PhD proposal uses ¹H Magnetic resonance spectroscopy (MRS) which is a non-invasive method capable of making measurements of human neurochemical profiles to improve our understanding of the biological basis of the most common form of tinnitus: hearing-loss related subjective tinnitus.

Preliminary evidence supports the utility of MRS as a tool for studying tinnitus and for bridging the gap between animal and human models of hearing loss and tinnitus.^{3,4} To date, there has been one MRS study of human hearing loss³ which observed lower GABA+ concentrations (GABA with macromolecular contamination) in a hearing impaired group (n=16) compared to age-matched controls (n=20) in the auditory cortical region, and one MRS study of human tinnitus⁴ which observed lower GABA+ concentration in a tinnitus group (n=14) compared to age and hearing loss-matched controls (n=14) in the auditory cortical region.

Aims:

This project aims to measure the chemical makeup of the hearing and emotional brain; both known to play a role in tinnitus.

1. Are tinnitus-specific changes in the way the brain is working limited to the central auditory system (hearing brain), or do they extend to the non-auditory network involved in tinnitus distress (emotional brain), in the same way as chronic pain?⁵ If brain changes are extensive, then this would suggest that the drug development process needs to consider classes of drugs that act broadly across the brain, or to explore combinations of active ingredients.

2. Do tinnitus-specific changes differ between acute and chronic tinnitus?

New information could be used as a possible guide to developing selective pharmacotherapy for subjective tinnitus, while also serving as an objective metric to evaluate the effectiveness of drug-based, device-based or psychologically informed interventions. If brain changes are dynamic, then this would suggest that drug development needs to target particular subgroups of people according to tinnitus duration.

Methodology:

To give a more precise measure of metabolites than ⁴, we will use a smaller volume of interest, individually optimise the position of the volume of interest over primary auditory cortex using a short 'localiser' fMRI protocol. To achieve greater statistical robustness we will also recruit a larger sample size.

We will use the UoN MR system with novel MRS sequences developed and optimised at Nottingham. A localised ¹H MRS direct detection method with short echo time (TE) will be used to measure the concentration of a broad-range of metabolites, including GABA+, NAA, Cr, and phosphocreatine (PCr). NAA is of interest because it is an established marker of neuronal injury or loss and has been shown to reduce following auditory deafferentation (Kilicarslan et al., 2014). PCr and Cr are involved cell energy metabolism. The concentration of total Cr 'tCr' (i.e. PCr + Cr) is relatively stable in the brain and thus often used as an internal reference for quantification. ⁶

Informed by power estimations, we will recruit 30 participants in acute/subacute tinnitus, chronic tinnitus, and normally hearing control groups. Participant groups will be matched for age, gender and hearing loss. Patients will undergo a full "audiological workup" with tests of hearing and tinnitus, as well as some questionnaires to assess general health and emotional well-being.

Benefits and suitability as a PhD project:

The supervisory team brings together expertise in hearing science, radiological medicine and MR physics to make the most of the cutting-edge technology that is locally available. The imaging techniques have been fully validated on the Nottingham scanners ⁷ and applied to address neuroscientific questions in chronic pain populations. While the PhD aims are relatively exploratory in tinnitus, Sedley's project ⁴ was completed as part of a PhD (University of Newcastle).

A risk assessment has identified contingency plans for potential problems.

References(bold=UoN):

1. **McCormack et al. Hear Res. 2016;337:70-9.**
2. **Baguley et al. Lancet 2013;382(9904):1600-7.**
3. Gao et al. *NeuroImage* 2015;106:311-316.
4. Sedley et al. *J Neurosci.* 2015;35(44):14822-8.
5. **Cottam et al. Neuroimage Clin. 2016;12:269-76.**
6. Stagg & Rothman 2013. *Magnetic resonance spectroscopy.* Academic Press.
7. **Napolitano et al. MRM. 2013;69(6):1528-3.**

Section 2 – Training Provision:

Locally, the student will benefit from being part of the NIHR Nottingham BRC, 'Imaging' Beacon, School of Physics and Astronomy and DCN. We also offer national and international opportunities for added value.

Local:

- i) The NIHR Nottingham BRC provides the catalyst for reviewing and updating the N-Trans PhD training that is available to all SoM PhD students. In particular, its Director (Hall) plans to include BRC-theme specific training credits and these will include new training modules on hearing science and translational imaging.
- i) The two SoM supervisors are Head of two DCN groups in 'Otology and hearing' and 'Academic Radiology' respectively, thus being best placed to signpost the student towards training opportunities beyond those in the SoM N-Trans programme. The Beacon focuses UoN strategy towards maintaining excellence in Imaging in Precision Medicine. The student will thus benefit from the increase in research activity which provides an informal yet important multi-disciplinary learning environment.
- ii) Dr Chen Chen's involvement in supervision will bring additional training benefits by enabling the PhD student to access appropriate training modules on offer with the School of Physics & Astronomy.

National:

- iii) Excellent NIHR residential courses are available only to NIHR trainees (i.e. those registered for a higher degree and supported by a supervisor whom is in receipt of NIHR funding).

International:

- iv) A prestigious 4-year H2020 Marie Curie Innovative Training Network 'European School in Interdisciplinary Tinnitus' research commences in 2017. Deborah Hall is the Training Co-ordinator and a PhD supervisor.